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Smoking Cessation and Arrhythmic Death: The CAST Experience

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Objectives. **This study was performed to assess the effect of cigarette smoking cessation on overall mortality and the incidence of arrhythmic death in the population of the Cardiac Arrhythmia Suppression Trial (CAST).**

Background. **Cigarette smoking is a known risk factor for sudden cardiac death. Some of the adverse effects of smoking have been shown to dissipate with smoking cessation, but the time frame over which these changes occur and the population that stands to benefit have not been well delineated. CAST was a multicenter double-blind placebo-controlled study to determine whether suppression of ventricular ectopic activity by means of antiarrhythmic drugs in patients with left ventricular dysfunction after acute myocardial infarction would reduce the incidence of arrhythmic death.**

Methods. **Of 2,752 patients randomized to blinded therapy, 1,026 were smoking at the time of their baseline examination and completed a 4-month follow-up visit. Of these, 517 stopped smoking by the time of this visit ("quitters") and 509 continued to smoke ("smokers").**

Results. **Over a mean follow-up period of slightly <16 months, there were 17 arrhythmic deaths and 32 total deaths among the quitters versus 30 and 45, respectively, among the smokers; these differences were of marginal statistical significance. Most of the fatal events occurred in a group at high risk of ongoing ischemia: the 558 patients who did not have thrombolysis or undergo revascularization after their qualifying myocardial infarction. In this high risk cohort, smoking cessation greatly reduced the incidence of arrhythmic death and was associated with a statistically significant benefit in survival.**

Conclusions. **Smoking cessation was accompanied by a marked reduction in arrhythmic death and overall mortality that achieved statistical significance in a high risk cohort. These data imply that smoking cessation is important in risk factor reduction in patients with advanced ischemic heart disease.**

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Cigarette smoking is a known risk factor for acute myocardial infarction and sudden cardiac death, but its role in the pathogenesis of these events is incompletely understood (1–9). Cigarette smoke is a complex mixture containing several ingredients that could be deleterious to the cardiovascular system. In particular, nicotine produces a marked elevation in serum catecholamine concentration that is potentially arrhythmogenic, especially in persons with ischemic heart disease. Some of the adverse cardiovascular effects of cigarette smoking have been shown to dissipate with smoking cessation (10–16). The present study was planned prospectively to investigate the effect of smoking cessation on mortality and the incidence of arrhythmic death in the subjects of the Cardiac Arrhythmia Suppression Trial (CAST), a large cohort of high risk patients with frequent ventricular ectopic activity and left ventricular dysfunction after acute myocardial infarction.

Methods

The institutional committee on human research approved the study protocol in all participating institutions. A detailed description of the CAST methodology has been provided elsewhere (17–19). The initial part of the trial (CAST I), in which encainide and flecainide and moricizine were used, was begun on June 13, 1987 and was terminated on April 14, 1989. The CAST II trial, using three doses of moricizine, began on April 19, 1989, and was terminated on August 1, 1991. The following is a brief review of the more important aspects of the trial with more detailed information in the areas relevant to the present analysis.

Patients. Patients <80 years of age were eligible for CAST I if they demonstrated an average of ≥6 ventricular premature depolarizations/h on a baseline 24-h Holter ambulatory electrocardiogram (ECG) and were found to have an ejection fraction ≤55% within 90 days or ≤40% within 2 years of a documented acute myocardial infarction. Specifically excluded were patients with ≥15 consecutive beats of ventric-

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ular tachycardia at a rate of ≥120 beats/min >6 days after the infarction, patients with high grade atrioventricular block or symptomatic sinus node disease (in the absence of a permanent pacemaker) and those with conditions likely to limit life span (e.g., inoperable malignant neoplasm). Also excluded were patients receiving other antiarrhythmic drugs or those with contraindications to any of the study drugs.

Eligibility criteria for CAST II were similar except that patients could only be recruited up to 90 days after acute myocardial infarction (using the same Holter criteria as in CAST I) and only if the left ventricular ejection fraction was ≤0.40. In addition, disqualifying ventricular tachycardia was redefined to include runs ≤30 s at a rate of ≤120 beats/min unassociated with symptoms.

Open label titration in CAST I. After giving written informed consent, patients underwent an open label titration phase (averaging 15 days), during which up to two oral doses of three drugs (encainide, flecainide and moricizine) were evaluated. The titration was stopped as soon as a drug and dose were found that suppressed the arrhythmias. The criteria for suppression of arrhythmia were ≥80% reduction of ventricular premature depolarizations and ≥90% reduction of runs of unsustained ventricular tachycardia as measured by 24-h Holter recording. Patients whose arrhythmia increased during the open label titration or who were intolerant of the drugs were not advanced to the randomized phase of the trial.

Drug titration in CAST II. Baseline clinical data were recorded, and patients were randomized to receive either low dose moricizine or its matching placebo for a 2-week period. This initial blinded, placebo-controlled, short-term exposure phase of the trial evaluated only the 1st 2 weeks of therapy. After 2 weeks, therapy was unblinded and the patients who had been treated with active medication were evaluated by ambulatory ECG recording to determine whether ventricular premature depolarizations were adequately suppressed. In patients who had been treated with placebo (or delayed initiation of active therapy), active moricizine titration was begun and followed by evaluation with ambulatory ECG recording.

Patients who had been treated with moricizine or matching placebo in CAST I simply continued their assigned treatment in CAST II. Patients who had been assigned to receive encainide, flecainide or placebo in CAST I and whose ectopic activity persisted after discontinuation of their assigned treatment were offered the opportunity to participate in CAST II and underwent the blinded 2-week trial as just described.

Adequate suppression of ventricular premature depolarizations was defined as in CAST I. Three doses of moricizine were available for titration and if adequate suppression was not obtained with the initial dose, the second and, if necessary, the third dose were used as long as disqualifying adverse effects or symptoms did not occur.

Randomization and follow-up. Patients whose arrhythmias were suppressed were randomly assigned (in double-blind manner) to receive the dose of the drug that suppressed their ventricular ectopic activity or matching placebo by strata based on clinical center, left ventricular ejection fraction and length of time between the index myocardial infarction and the qualifying Holter recording. Patients were seen in follow-up at 4-month intervals.

Study design. Of the total of 2,752 patients who were randomly assigned to blinded therapy, 1,115 were smoking at the time of their qualifying myocardial infarction. Of these, 1,026 had a complete 4-month follow-up visit and are the subject of the present report. Of the remaining 89 patients, 29 (2.6%) died before their 4-month follow-up visit, 5 (0.4%) withdrew from the study, 33 (3.0%) had not had the scheduled 4-month visit by the time the study ended and 22 (2.0%) had incomplete follow-up information. Smoking status (including the number of cigarettes smoked) was determined by the physician or nurse coordinator at the time of the baseline examination, at the 4-month follow-up visit and yearly thereafter. For the purpose of the present analyses we defined "quitters" as persons who stopped smoking between the time of their qualifying myocardial infarction and their 4-month follow-up visit and "present smokers" as those who continued to smoke until that time. In keeping with the original CAST hypothesis, our primary study end point was arrhythmic death/resuscitated cardiac arrest (subsequently referred to as arrhythmic death) and our secondary end point was total mortality/resuscitated cardiac arrest (subsequently referred to as total mortality). For purposes of analysis, arrhythmic death included witnessed instantaneous death, unwitnessed death with no preceding change in symptoms for which no other cause could be ascribed, resuscitated cardiac arrest or witnessed death with anginalike symptoms or symptoms suggestive of a cardiac arrhythmia (e.g., syncope, palpitation or dizziness) in the absence of severe congestive heart failure or shock.

Statistical methods. The clinical and demographic characteristics at baseline were compared for the present smokers and the quitters by using standard chi-square statistics and *t* tests. Kaplan-Meier survival curves (17) with Mantel-Haenszel (17) log rank statistics were used to compare the rate of arrhythmic deaths and total mortality occurring in the two groups over the course of the CAST study.

To control for baseline differences between the two groups, Cox proportional hazards models (17) were used to consider the two end points: arrhythmic death and total death. The following explanatory variables were included in each model: age, gender, ejection fraction (assessed by either ventriculography, nuclear techniques or echocardiography), history of myocardial infarction (before the CAST qualifying myocardial infarction), history of congestive heart failure (assessed by standard clinical criteria with use of the New York Heart Association classification) and CAST treatment group (active treatment vs. placebo), history of diabetes, history of coronary artery angioplasty or bypass grafts, the use of thrombolytic agents during the CAST qualifying myocardial infarction, coronary artery bypass surgery after the qualifying myocardial infarction, the rate of ventricular premature depolarizations/h, the presence of new anterior Q waves, the presence of cardiac complications during the baseline hospital stay, baseline use of calcium channel blockers and the smoking status variable.

These variables were included either because they are known to be associated with arrhythmic mortality in CAST or because they differ significantly for smokers and quitters. Because some patients changed their smoking status after the 4-month follow-up period, "smoke" was made a time-dependent variable that changed if a patient reported a different smoking status at a subsequent follow-up. Thus, patients who had stopped smoking by the time of their 4-month follow-up visit but had started again and were active smokers at the follow-up visit preceding death were first counted as quitters and then, after they started smoking, as smokers. Similarly, patients who smoked through the time of their 4-month visit were first counted as smokers and then as quitters if they were no longer smoking at the clinic visit before death. Because smoking status was highly associated with revascularization at the time of the CAST qualifying myocardial infarction, the effect of smoking was considered separately for patients who did or did not have thrombolysis or bypass surgery at the time of the qualifying infarction.

The data were examined in several patient subgroups based on the following variables: age, gender, history of myocardial infarction (before the qualifying infarction), history of congestive heart failure, history of diabetes mellitus, treatment group (active medication or placebo), ejection fraction and the presence of runs of ventricular tachycardia on the qualifying Holter recording. Unadjusted arrhythmic death rates were compared for the various subgroups by using chi-square statistics. Throughout this report, results are considered statistically significant when $p < 0.05$ except for the subgroup analyses, when $p < 0.01$ is required for statistical significance.

Results

Table 1 shows the baseline clinical and ECG characteristics of our study sample. Of the 1,026 patients who were active smokers up to the time of their qualifying myocardial infarction, 517 stopped smoking before their 4-month follow-up visit ("quitters") and 509 continued smoking (present "smokers"). The groups are comparable in a wide variety of characteristics but show some differences. For example, a significantly higher proportion of present smokers had a previous history of myocardial infarction and congestive heart failure whereas a higher proportion of quitters had a new anterior wall myocardial infarction, had received thrombolytic agents, had periinfarct complications and had coronary artery bypass surgery after their CAST qualifying myocardial infarction. The mean follow-up period was 497 ± 366 days for the quitters and 488 ± 357 days for the smokers.

As assessed by the 4-month smoking status, the quitters had 17 arrhythmic deaths and 32 deaths overall, whereas the smokers had 30 arrhythmic and 45 total deaths. Survival curves comparing the smokers and quitters are significantly different for arrhythmic death/cardiac arrest ($p = 0.04$, Fig. 1) and display a trend for total survival ($p = 0.066$, Fig. 2). After 2 years, the estimated rate of survival from arrhythmic death for smokers versus quitters was 89% versus 94%; for total survival, the figures were 85% and 91%, respectively.

By univariate Cox regression analysis, continuing to smoke is highly associated with arrhythmic and total mortality ($p = 0.0078$ and $p = 0.12$, respectively). However, after adjustment for additional covariates in the multivariate Cox proportional hazards models, and using smoking as a time-dependent variable (104 of 1,026 patients [10.1% of the sample] changed smoking status during the follow-up period), the association between continuing to smoke and arrhythmic and total mortality is of only marginal statistical significance ($p = 0.095$ and $p = 0.062$, respectively). The hazards ratio is 1.80 (95% confidence interval [CI] 0.88 to 3.67) for arrhythmic mortality

Table 1. Baseline Characteristics of the Study Group

	"Quitters" (n = 517)	"Smokers" (n = 509)	p Value
Age (yr)	58.5 ± 10	57.0 ± 10	NS
Male	81.8%	85.3%	NS
CAST active treatment	50.5%	51.5%	NS
Prior MI	29.6%	39.7%	0.001
Prior CHF	8.3%	14.3%	0.002
Hypertension	28.0%	28.1%	NS
Diabetes	14.3%	13.9%	NS
Smoked 1 to 20 cigarettes daily	—	83.7%	—
Cigarettes smoked at baseline (no.)	25.3	23.7	NS
Qualifying ECG			
Heart rate (beats/min)	74.3 ± 16	74.5 ± 14.4	NS
ST depression ≥1 mm	28.7%	29.2%	NS
New anterior Q waves	30.1%	20.1%	0.001
QT interval (s)	0.385 ± 0.04	0.385 ± 0.04	NS
Qualifying Holter			
VPD/h (no.)	118 ± 231	148 ± 288	NS
VT runs present	23.8%	27.3%	NS
Median time from qualifying MI to qualifying Holter (days)	41.0	40.0	NS
Ejection fraction	36.5 ± 10	36.7 ± 10	NS
Prior CABG/PTCA	11.2%	19.4%	0.001
Complications during hospital stay	31.4%	21.2%	0.001
Thrombolytic agents since MI	37.7%	28.9%	0.003
PTCA since MI	19.0%	20.0%	NS
CABG since MI	21.3%	13.4%	0.001
Beta-blockers	29.2%	30.3%	NS
Calcium channel blockers	41.8%	50.5%	0.01
Digitalis	22.2%	20.4%	NS
Diuretic drugs	30.4%	32.8%	NS

Unless otherwise indicated, data are presented as mean value ± SD or percent of patients. CABG = coronary artery bypass graft surgery; CAST = Cardiac Arrhythmia Suppression Trial; CHF = congestive heart failure; ECG = electrocardiogram; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; VPD = ventricular premature depolarizations; VT runs = three or more consecutive ventricular premature depolarizations at a rate ≥120 beats/min.

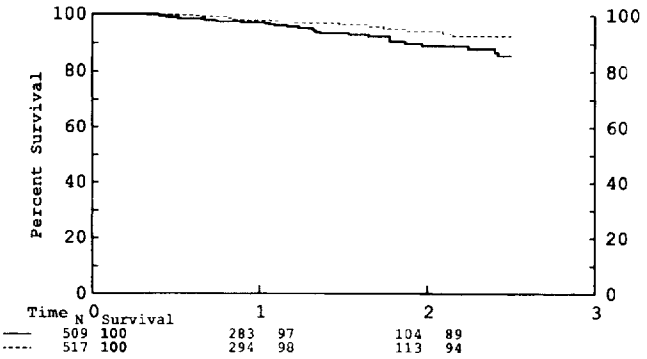

Figure 1. Kaplan-Meier curves for survival free of arrhythmic death or resuscitated cardiac arrest for present "smokers" **(solid line)** and "quitters" **(dashed line)**. Time is measured in years; N refers to the number of patients at risk at 0, 1 and 2 years; and Survival is the Kaplan-Meier estimate of survival from arrhythmic death or resuscitated cardiac arrest at 0, 1 or 2 years. The two curves are significantly different (log rank statistic 4.21, p = 0.040).

and 1.64 (95% CI 0.97 to 2.79) for total mortality. Specifically, the use of thrombolytic agents at the time of the qualifying myocardial infarction or subsequently undergoing coronary artery bypass surgery, or both, appears to be a confounding covariable. In fact, the 558 patients who underwent neither of these interventions constituted an especially high risk subset with 62 deaths (38 arrhythmic) compared with only 15 deaths among the 468 patients having one or both interventions (the 558 patients with no intervention do appear to be older and "sicker" with a significantly lower ejection fraction and a higher incidence of angina, diabetes, diuretic use, atrial arrhythmias, premature ventricular beats, history of congestive heart failure and prior myocardial infarction) (Table 2). We examined smoking cessation in this high risk cohort by using the multivariate Cox proportional hazards model where we controlled for the same variables in the high risk cohort as we did for the entire group. In this model, smoking cessation

Figure 2. Kaplan-Meier curves for survival free of death or resuscitated cardiac arrest (total mortality) for present "smokers" **(solid line)** and "quitters" **(dashed line)**. The two curves are not significantly different but show a trend (log rank statistic 3.37, p = 0.066). Format as in Figure 1.

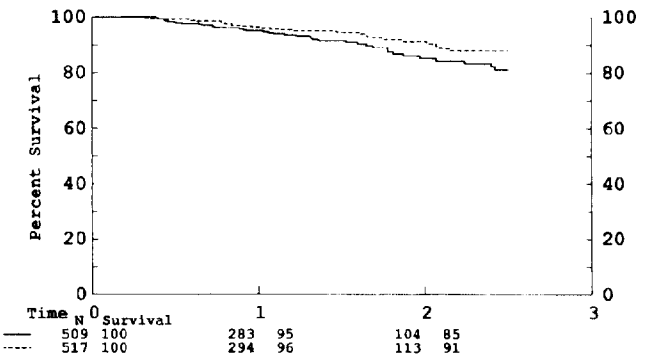

Table 2. Baseline Characteristics of the High Risk Cohort

	"Quitters" (n = 246)	"Smokers" (n = 309)	p Value
Age (yr)	59.6 ± 10	58.7 ± 10	NS
Male	79.4%	83.5%	NS
CAST active treatment	51.6%	50.6%	NS
Prior MI	31.5%	43.2%	0.001
Prior CHF	10.9%	17.4%	0.03
Hypertension	30.2%	30.6%	NS
Diabetes	19.0%	15.8%	NS
Qualifying ECG			
ST depression ≥1 mm	32.5%	30.2%	NS
New anterior Q waves	26.4%	20.2%	NS
QT interval (s)	0.386 ± 0.043	0.389 ± 0.042	NS
Qualifying Holter			
VPD/h (no.)	139 ± 282	156 ± 279	NS
VT runs present	22.3	25.1	NS
Ejection fraction (%)	36.4 ± 11	36.1 ± 11	NS
Prior CABG/PTCA	12.9%	19.0%	NS
Complications during hospital stay	28.5%	21.4%	NS
Beta-blockers	31.5%	30.0%	NS
Calcium channel blockers	50.4%	58.1%	NS
Digitalis	20.2%	19.4%	NS
Diuretic drugs	33.9%	38.4%	NS

Unless otherwise indicated, data are expressed as mean value ± SD or percent of patients. Abbreviations as in Table 1.

appears to be of major benefit (p = 0.067 for arrhythmic deaths and p = 0.012 for total mortality). In the high risk cohort, the hazard ratios for continuing to smoke are 2.06 (95% CI 0.92 to 4.61) for arrhythmic mortality and 2.13 (95% CI 1.16 to 3.91) for total mortality. The small number of fatal events in the patients who had thrombolysis or bypass surgery (the "low risk" cohort) precludes meaningful statistical analysis.

With two exceptions, there were fewer arrhythmic deaths among the quitters in all other subgroups examined, and this difference was especially prominent in patients with an ejection fraction <30% and in patients with runs of ventricular tachycardia on the baseline Holter ECG. Among women and patients with diabetes, those classified as quitters had slightly more arrhythmic deaths than those classified as smokers, but both of these subgroups were extremely small.

Discussion

The major finding of the present study is that the benefits of smoking cessation are apparent, even in a relatively brief follow-up period, in a sample selected specifically for high risk of arrhythmic death. The negative outcome of the patients receiving active treatment (antiarrhythmic drugs as opposed to placebo) has been reported previously (18–20). It is interesting, then, that the beneficial effects of smoking cessation appear to be comparable in the placebo and the active treatment groups. Although smoking cessation was associated

with a marked reduction in overall mortality and arrhythmic death, this decrease was relatively unimpressive in patients who had received thrombolytic agents in the course of their qualifying myocardial infarction or had subsequently undergone coronary artery bypass surgery, or both, perhaps because of the very small number of events in this subgroup. In contrast, patients who had neither of these interventions exhibited a major benefit from smoking cessation. Similarly, quitters with a low ejection fraction and those with runs of ventricular tachycardia on the baseline Holter ECG, who also constitute a high risk subset, had an especially good outcome compared with that of patients who continued smoking.

These findings imply that smoking cessation is of particular benefit to patients at highest risk of arrhythmic death, and they suggest an interaction between an arrhythmogenic substrate and the deleterious (and presumably proarrhythmic) effects of cigarette smoking. Thus, smoking cessation would appear to be a particularly important aspect of risk factor modification in patients with the most advanced ischemic heart disease. Beneficial effects of smoking cessation were not observed in women, or in patients with diabetes. However, the small number of patients in these two subgroups precludes definitive conclusions. Of interest is work by Moy et al. (21) and Howard and Howard (22), who found cigarette smoking in diabetic women to have an especially negative prognostic impact. Perhaps the adverse effects of smoking in this group of patients persist for a longer period of time.

Cigarette smoking has been demonstrated to produce a variety of harmful cardiovascular effects that may be attenuated or even reversed by smoking cessation. Smoking has been shown to increase platelet adhesiveness and serum fibrinogen levels, to decrease high density lipoprotein cholesterol levels, to transiently diminish the lumen diameter of coronary arteries and to increase the rate of atherogenesis, in part by the generation of carbon monoxide, a substance that interferes with oxygen transport and may directly injure vascular endothelium (7,23–29). Cardiovascular mortality and the incidence of acute myocardial infarction have been shown gradually to diminish after smoking cessation, both in subjects with and without clinically manifest ischemic heart disease (9–16). Similarly, Hallstrom and coworkers (29) describe 310 persons with aborted sudden cardiac death whose recurrence rate over a 4-year (mean) follow-up period was related to continued smoking. The relation between cigarette smoking and arrhythmias is less clear. Davis et al. (30) used 24-h ambulatory ECG monitoring to evaluate the effects of 1 h of smoking and failed to find any relation between cigarette smoking and ventricular arrhythmias. Our study documents a marked reduction in overall mortality and the incidence of arrhythmic death over a 1-year (mean) period in a large cohort of particularly high risk persons. It is possible that other factors, such as acute myocardial ischemia and increases in sympathetic nervous system tone, may interact synergistically with smoking to initiate the fatal event.

Limitations of the study. Our data must be interpreted in the light of certain methodologic limitations. The positive effects of smoking cessation for our entire study group was of marginal statistical significance, with major benefit occurring primarily in those persons at highest risk. Thus, our study did not have sufficient power to detect a difference in outcome between the two major study groups. Similarly, the low event rate in lower risk patients precludes any definitive statement about the benefits of smoking cessation in this group. Future studies involving a larger number of patients and a longer follow-up period will be necessary to determine whether smoking cessation is beneficial in all patients after myocardial infarction or merely in selected subgroups. Our classification of quitter or present smoker was based solely on patient interviews and not confirmed by serum nicotine or cotinine concentrations. It is probable that this bias may, if anything, have caused an underestimation of the benefits of smoking cessation because it is more likely that patients would underestimate the number of cigarettes smoked or underreport continued smoking (continue to smoke surreptitiously) than they would underreport smoking cessation. Our definition of quitters is necessarily somewhat arbitrary—that is, those who stopped smoking between the time of their qualifying myocardial infarction and their 4-month follow-up visit. Because the length of time required for the adverse effects of smoking to dissipate is unknown, it is possible that some of the events among the quitters were smoking related.

Unlike some workers, we failed to find a relation between fatal events and the number of cigarettes smoked, perhaps because 84% of our patients smoked ≤ 1 pack of cigarettes daily. Another study limitation is that serial 24-h ambulatory ECGs were not obtained routinely during the follow-up period. Correlation of smoking status with the frequency of arrhythmias would be instrumental in delineating the relation between smoking and arrhythmic death. We did obtain 24-h ambulatory ECGs at the 4-month follow-up visit in a randomly selected subset of patients (there were 112 smokers and 122 quitters in this subset) and found a slight trend indicating that quitters had a greater decrease in ventricular ectopic activity during the 1st 4 months of CAST therapy than did smokers ($p = 0.11$). Lastly, our sample was highly selected so that our data may not be applicable to persons without ischemic heart disease, left ventricular dysfunction and frequent ventricular ectopic activity.

Summary and conclusions. In summary, our analysis of the large and carefully followed up population of the CAST study revealed that smoking cessation was accompanied by a major reduction in the incidence of arrhythmic death and total mortality. The reduction in mortality achieved statistical significance in the cohort at greatest risk of arrhythmic death. These data imply that cigarette smoking, probably in conjunction with other factors, may be dangerously arrhythmogenic, and they emphasize the importance of smoking cessation in risk factor reduction in patients with advanced ischemic heart disease.

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